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DR. ANDREW G. DU MEZ
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IN MEMORIAM

DR. ANDREW G. DU MEZ

THE death of Dr. Du Mez on September 27, 1948 was a tragedy to his many friends and a serious loss in the field of pharmaceutical education.

Andrew G. Du Mez was born in Horicon, Wisconsin, on April 26, 1885. His early education was obtained in the public schools of Cashton, Wisconsin. Later he attended the University of Wisconsin and received the degrees of graduate in pharmacy, bachelor of science, master of science and, finally, the doctor of philosophy. He served at the university as an instructor in pharmaceutical chemistry; later he became professor of chemistry at the Oklahoma Agricultural and Mechanical College. From 1912 to 1916 he was director of the School of Pharmacy at the University of the Philippines. Here he also served on a committee to revise the pharmacy laws of the Islands.

In 1917 Dr. Du Mez was appointed as associate pharmacologist in the Hygienic Laboratory of the U. S. Public Health Service. He left this field to become dean of the University of Maryland School of Pharmacy in 1926, a position he held until his death.

Among the many important contributions made to American Pharmacy by Dr. Du Mez, the foremost was his painstaking efforts in raising the standards of pharmaceutical education. As secretary-treasurer of the American Council on Pharmaceutical Education upon him fell much of the burden of this accrediting agency.

Dr. Du Mez served a term as president of the American Pharmaceutical Association and as president of the American Association of Colleges of Pharmacy. He was a member of the Council of the A. Ph. A. for two decades and a member of the Revision Committee of the United States Pharmacopoeia since 1920. Many other positions of responsibility had been and were held by Dr. Du Mez throughout the wide field of pharmacy.

Dr. Du Mez by reason of his outstanding contributions to American Pharmacy had been selected to receive this year its highest

honor, the Remington Medal. It is tragic indeed that it must be awared posthumously and that he did not live to receive the acclamation of his friends at a Remington Medal Banquet. A memorial service in Baltimore will take its place.

As vice-chairman of the Pharmaceutical Survey Committee, Dr. Du Mez was a key figure in the two-year study made by this group. It was during the final sessions of this Committee that Dr. Du Mez was stricken. His loss is indeed a blow to the implementation of the Committee's recommendations. Although his death was untimely, Dr. Du Mez must have known of the precarious state of his health. He preferred, however, to work to the very end in behalf of the profession to which he had dedicated his life.

E D I T O R I A L

A SIX-YEAR COURSE IN PHARMACY

ONE of the recommendations that seems certain to be made by the Pharmaceutical Survey in its final report is that the time has come when serious consideration should be given to the need for increasing the educational requirements of the pharmacist. A suggested six-year program of study would comprise two years of pre-professional collegiate training in a college of arts and sciences followed by four years of professional study leading to a doctor of pharmacy degree. Some excellent arguments are presented for this plan, chief among which is that the pharmacist if he is to be a full-fledged ally of the physician must have equal professional training as to quality. Anything short of this is likely to stamp him as inferior and frustrate his efforts to attain professional recognition.

There is little that can be said to refute the validity of this argument and the failure of many pharmacists to realize the prestige they would like to enjoy can be traced to an educational inadequacy that can be overcome by the individual concerned only by the expenditure of great time and effort. More and more does the pharmacist need a knowledge of chemistry, physics, pharmacology, etc. not just equal to the physician's but superior to it if he is to give full professional service.

From the idealistic standpoint there can be no doubt that a six-year program would train superior pharmacists—men and women who could serve in the highest professional sense as allies of the physician. The problems that concern many administrators in colleges of pharmacy are twofold. First, many colleges are not prepared as to facilities and personnel, to give such a course and neither is there a likelihood that they could become so prepared. Second, many administrators are concerned over the impact of such a program on the practice of pharmacy as we know it today. Retail pharmacy today absorbs over fifty per cent of the graduates of the colleges. Will men spending six years in obtaining a pharmaceutical degree be content with the financial return and the opportunity for

professional activity offered by retail pharmacy or will it be below their horizon? If the supply of men available in the retail field is reduced below a critical level, drug stores must perforce close. Since the public demands convenient retail outlets their place will be taken in all likelihood by patent medicine stores. Is the public better off then to have much of their service rendered in many instances by stores staffed with those having no pharmaceutical training? This is a serious problem and it is doubtful if anyone can provide a reliable answer. If the graduate were to serve only in some branch of the government, in hospitals, in strictly professional stores, and as company representatives, the six-year program would be the answer. For the average retail drug store the six-year program would appear to be in serious doubt.

Some administrators are considering the possibility of offering two types of training, the four-year program and the six. On the surface this seems to be the answer but it is fraught with serious objections academically. The whole concept of the six-year program is that the student will be more thoroughly grounded in the basic sciences before starting his professional courses. One of the disadvantages of the four-year course is that the student must take basic science and professional work concurrently. If a college attempts to give both programs, professional courses, if taught to a class composed of both types of students, will of necessity be taught at the lower level. If taught separately it would double the work of the professional departments and lead to confusion, administrative difficulties and great expense. It would seem therefore that one or the other program, not both, should be given.

If, as now seems likely, some schools give a six-year program and others retain the four-year program, serious complications may result. Both the Colleges and their graduates will be divided into two "armed" camps with friction and disunity the final result. In the end one or the other will win out but great damage might result to pharmacy in the process. It is unfortunate that a definite stand cannot be taken now for one program or the other by American pharmacy rather than hedging on the issue.

Probably the one factor which is the greatest unknown in the whole picture is the change that may be forthcoming in the field of medical care. The recent report to the President made by the Federal Security Administrator, Oscar Ewing, strongly recom-

mends a form of prepaid medical care under government sponsorship. Although the Murray-Wagner-Dingell Bill was defeated some time ago it is not altogether unlikely that some such plan may come to pass in the not too distant future. If and when it does, this may change very dramatically the picture of pharmacy. Self-medication and home remedies will give way to prescriptions and the drug store as we know it may change radically. Should this take place, six-year men would definitely be in a favorable position and their need increased.

All in all, it is next to impossible for one who is fair and open-minded to arrive at an exact opinion concerning the proposal for a six-year course. Under these circumstances we predict a plethora of debate from its proponents and opponents. In fact the debate may well become the leading argument of the decade, with its outcome at this point uncertain indeed.

L. F. Tice

DISINFECTION AND ANTISEPSIS: TRENDS AND IDEAS

(Part II)

By Emil G. Klarmann, D. Sc.

[Editor's Note. Last month we presented the first part of this excellent review by Dr. Klarmann. Its length made its inclusion in one issue impossible. References 1-113 will be found at the end of the first part in the September issue.]

Furacin

A SYNTHETIC antiseptic which has gained some prominence in the recent past is 5-nitro-2-furaldehyde semicarbazone introduced under the name of "Furacin" (114). Its chemical character constitutes somewhat of a departure from that of the more important and better known classes of antiseptic products. According to Dodd and Stillman (115), it is both bactericidal and bacteriostatic for a variety of gram-positive and gram-negative pathogens. It retains its activity in the presence of body fluids (116), and upon oral administration it is claimed to produce a therapeutic effect in experimental infections of mice with a number of gram-positive and gram-negative microorganisms. It is possessed of low toxicity and irritant action (117); in fact, in ointment form it is less irritant than sulfathiazole or tyrothricin. Its practical usefulness in the treatment of ulcers was established by Downing, Hanson and Lamb (118) who also comment favorably upon its non-interference with granulation and epithelization. In the case of some abnormal skin there is the risk of sensitization, but not more so than by penicillin or sulfathiazole.

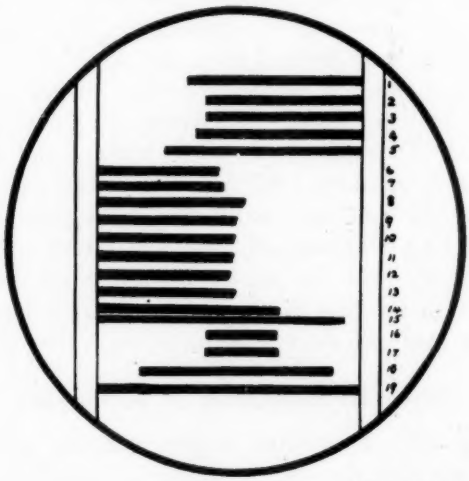
Other Developments in Antiseptics

A development of potential interest depends upon the recognition of the fact that the interference by p-aminobenzoic acid with the bacteriostatic action of sulfanilamide is not duplicated in the case of p-(aminomethyl)-benzene-sulfonamide, i. e., a compound which differs from the former in that a methylene grouping separates the amino group from the carbon atom of the benzene ring (119). This finding is especialy significant in view of repeated criticisms directed against the use of sulfanilamide (and of other sulfa-drugs) as wound antiseptics which appear to be well justified by Hartmann's (120) results obtained with localized pyogenic infections.

Another case of possible developmental interest is that of the organic tellurium compounds. In a recent paper (121) Fleming took the occasion to contrast the extraordinary bacteriostatic effect of penicillin upon gram-positive microorganisms, with that of sodium tellurite upon the gram-negative ones, emphasizing at the same time the great toxicity of sodium tellurite and expressing the hope that tellurium could be worked into a suitable derivative which would reduce its toxicity in the same fashion as, e. g., the arsphenamine structure affects the toxicity of arsenic. The following drawing (Fig. V) gives an illustration of the conditions obtained respectively with peni-

FIG. V

COMPARISON OF BACTERIOSTATIC POWER OF PENICILLIN AND POTASSIUM TELLURITE (FLEMING)



Penicillin Potassium Tellurite

Penicillin gutter on left. Tellurite in gutter on right. Organisms streaked across between gutters. Black line shows limit of growth.

Organisms:

1 Staphylococcus.
2 Streptococcus hæmolyticus.
3 Pneumococcus.
4 Streptococcus viridans.
5 Diphtheria bacillus.
6 Brucella abortus.
7 B. typhosus.
8 R. dysenteriæ.
9 B. coli.
10 V. choleræ.
11 B. pestis.
12 B. influenzæ.
13 B. pertussis.
14 B. pyocyaneus.
15 B. proteus.
16 Gonococcus.
17 Meningococcus.
18 B. anthracis.
19 Enterococcus.

cillin and sodium tellurite. It is noteworthy, therefore, that according to Gulland and Farrar (122) certain substituted cyclotelluropentanedione derivatives are bactericidal for *E. coli* to an extraordinary degree (e. g., the 2,4-dimethyl derivative in a dilution of 1:5,000,000, the 2,6-dimethyl derivative in one of 1:9,000,000). Similar results were obtained with *E. typhosa,* and incidentally with staphylococci and streptococci, attesting to the absence of specificity in this class of compounds.

General Comment

With respect to the several desiderata whose simultaneous fulfilment would appear to stand in the way of developing the "ideal" wound antiseptic, some general obesrvations may be in order, at this point.

The ideal antiseptic would be one showing a maximum of bacteriotropic action and a minimum (or absence) of organotropic action. In other words, it would have to be strongly germicidal for all kinds of pathogens in a bodily environment, but harmless (or practically so) for the tissues with which it comes in contact. A chemical antiseptic answering this description does not exist; some antibiotics, e. g., penicillin, approach this ideal in certain, but not in all respects. The question arises: is such an ideal antiseptic actually needed, and does the search for it justify the effort?

In this connection, it may be pointed out that the chief value of a substance used as an antiseptic might reside occasionally in some other than its antibacterial effectiveness. As an example one could mention the Carrell-Dakin solution which at one time enjoyed considerable acceptance; yet Fleming claims that when this solution is introduced into a wound and removed after ten minutes, its antibacterial potency, as determined by the amount of available chlorine, drops below any inhibitory level (121). Since the Carrell-Dakin method specifies the instillation of the solution every two hours, it would appear that for periods of one hour and fifty minutes there is no effective antiseptic in the wound. Evidently, the proved success of the Carrell-Dakin treatment depends upon increased transudation from the wound, producing an unexpected drainage of stagnated fluid which has lost its antibacterial power, and causing its replacement by fresh lymph.

Since phagocytes form the first line of defense against bacteria in cutaneous lesions, one frequently meets with the demand that anti-

septics should not interfere with phagocytosis; in other words their attack should be directed against the invading bacteria, while leaving the phagocytes alone. Such a demand is entirely logical, yet there are hardly any chemical antiseptics in existence which in a practical concentration would leave the phagocytes untouched while destroying the infective microorganisms. (Again, there is an approach to such a behavior in the case of certain antibiotics). As a matter of fact, Fleming has shown how under proper experimental conditions, the concentration of phenol can be manipulated in such a fashion as to inhibit phagocytosis, with the seemingly paradoxical result that the addition of an antiseptic to blood infected with staphylococci will cause an increase in their number; of course, the reason is that in a given concentration, the activity of the leucocytes has been suppressed, thereby permitting survival of the staphylococci. A still further increase in the concentration of phenol will decrease the number of the microbes or eliminate them altogether owing to the direct action of phenol upon the bacteria. This phenomenon permits the theoretical assumption that an antiseptic may be placed in a wound in such a concentration as to affect the pus cells while leaving the invading microbes unhampered, at least until a new supply of leucocytes is delivered by the system to the wound to resume the defense against the bacteria.

A wound antiseptic is the more valuable, the less it interferes with the healing of the wound, and particularly with the processes of granulation and epithelization, other things being equal. With this in mind, it would appear permissible to use even a systemic poison as a wound antiseptic, provided that its general behavior in contact with wound tissue is known to be such as to eliminate the risk of systemic absorption in a quantity sufficient to produce a generalized toxic effect. But to what extent should one consider the antileucocytic action of practically all chemical antiseptics? It might help to arive at a decision in this matter if one were to remember that the action of a topical antiseptic is static and of short duration in contrast to the continuous, dynamic function of the human or animal organism in sending phagocytes to the site of the injury and of the origin of a potential bacteremia. Even if the antiseptic should interfere temporarily with phagocytic activity, it may be assumed that, applied correctly (particularly in a sufficient concentration), it would eliminate most of the invading microbes more rapidly than

would the leucocytes whose supply might not suffice to prevent the bacterial multiplication from getting out of control and producing a generalized infection from a wound which has become septic in character. To this extent, it would seem that the results of one of the several methods (123, 124, 125, 126) which measure the effect of antiseptics upon phagocytosis, may not supply the sole criterion of fitness of a particular preparation for wound therapy, and that such results should be considered only in combination with other factors in order to yield a conclusive pattern. In this connection, a distinction must be drawn also between single antiseptic applications and those involving continuous action as, e. g., irrigations, wet dressings, etc., for obvious reasons.

None of the above comments will apply to surface antiseptics coming in contact with the unbroken skin or with the mucous membrane (e. g., mouth antiseptics, vaginal douches, etc.) where phagocytosis is not involved. Nor do the observations on bactericidal vs. bacteriostatic action apply to the latter conditions, without additional qualification, since impairment of the bacteriostatic action by, e. g., specific reactive groupings (such as the sulfhydryl radical) need not be given too serious a consideration.

Antiseptic Soaps

In the recent past, there have been some noteworthy developments in the matter of antiseptic soaps. Although some of them were published under the heading of "germicidal soaps", it is felt that the attribute "antiseptic" is more proper in the light of the results obtained with these soaps.

In considering this subject in its proper perspective, it is well to remember that ordinary toilet soap, by virtue of its detergent action removes an appreciable number of bacteria from the skin, in addition to grime, oil, etc. Beyond this more or less mechanical capacity for removal of bacteria, soaps are possessed of definite antibacterial properties with respect to a number of pathogens; however, it would be misleading to refer to this action as being "disinfectant" or "antiseptic" in view of the fact that other organisms of pathogenic significance are highly resistant to their action. In the case of "chemically pure soaps," i. e., of compounds obtained by the neutralization of pure fatty acids, many regularities have been found in the relationship between their chemical constitution and their antibacterial action; thus, in the homologous class of soaps from saturated

fatty acids, the antibacterial action is a direct function of the length of the carbon chain, the position of maximum efficacy varying with regard to different microorganisms. For a review of literature on this and related matters, the paper by Klarmann (127) should be consulted. A subsequent paper by Klarmann and Shternov (128) deals with the effect upon several test organisms (*E. typhosa, S. paradysenteriae, S. aureus, Strep. pyog. hemol., Trichophyton rosaceum*) of the following three categories: a homologous series of potassium soaps of saturated fatty acids, a group of commercially available toilet soaps, and a number of "technical" soaps obtained by the saponification of fatty oils. Of the homologous series, only the salts of fatty acids with eight to ten carbon atoms evidenced a germicidal efficacy of some note. Since fatty acids of this description do not occur in the fats and oils used in soap making the antibacterial properties of the several commercial toilet soaps tested were neither expected nor found to be such as to merit the descriptive designations "germicidal," "disinfectant," or "antiseptic."

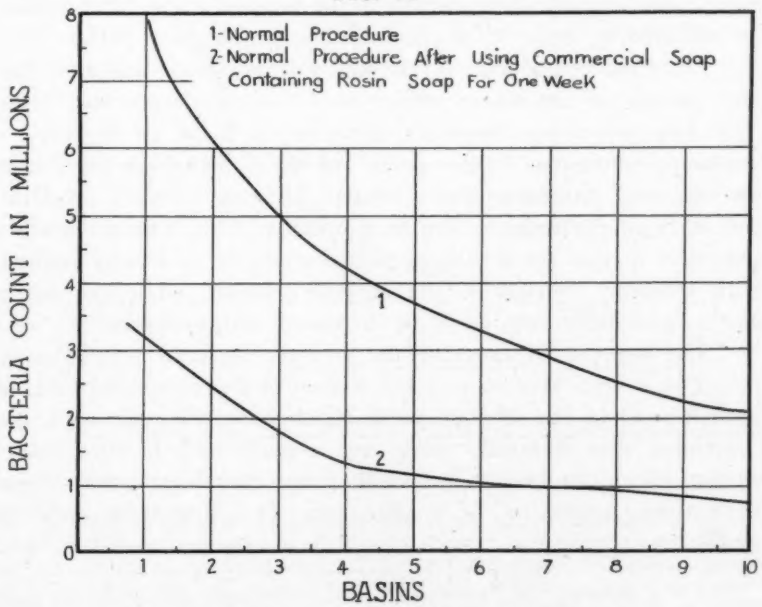
However, among the "technical" soaps, those obtained by the saponification of rosin were found to be active against staphylococci and streptococci, to a rather remarkable degree. Indications of an *in vitro* activity of rosin soap and of mixed fatty acid-rosin soaps were obtained previously by Walker (129). Unlike toilet soap which consists substantially of alkali salts of long chain fatty acids, rosin soap is derived from abietic acid and related compounds (some unsaponifiable), of a rather complex, partially saturated polycyclic structure.

Almost simultaneously with the publication of Klarmann's and Shternov's work on soaps, there appeared two papers by Stuart and Pohle (130, 131) one of which dealt with the antibacterial action of rosin soaps and mixed fatty acid-rosin soaps as observed in hand washing experiments patterned along the lines of Price's technique (132). On the basis of studies on the removal of bacteria by hand washing, Price had arrived previously at the conclusion that the microbial flora of the skin of the hands consisted of two distinct groups which he termed the "transient" and the "resident," respectively. While the former is readily removed by soap and water, the latter (inhabiting the lower skin layers and consisting mostly of staphylococci), is quite resistant to such removal. A series of consecutive washings in ten basins of soap solution, if described by a

graph, with the counts of bacteria removed as ordinate, and the number of basins as the abscissa, yields a curve which at first drops rather sharply (as a result of reduction of the transient flora), then flattens out asymptotically, indicating the stage at which the resident flora has been reached. Price has shown that little or no germicidal action is produced by toilet soaps in the course of this procedure, and that the count per basin (as determined by plating) indicates the actual number of organisms removed with each washing; those remaining on the hands after about three washings belong mostly to the resident flora.

Stuart and Pohle found, among other things, that if a rosin-soap was used regularly for one week, a washing test carried out with ordinary, i. e., rosin-free soap disclosed a substantial reduction not only of the transient but also of the resident bacterial flora. This effect is shown on the following graph (Fig. VI) in which curve 1 indicates the condition resulting from normal, washing procedure, whereas curve 2 is descriptive of the condition created by the use of a brown bar soap consisting in part of rosin soap. If regular

FIG. VI



"Degerming" action of rosin Soap (Stuart and Pohle).

toilet soap had been used instead, the second curve would have coincided with the first, on the basis of available evidence. From this it was concluded that wider consideration might be given to rosin soaps or to mixed fatty acid-rosin soaps where a farther reaching antibacterial effect was of interest.

The important work of Stuart and Pohle has been reviewed here in some detail because of the fundamental observation as to the possibility of depressing the resident skin flora, by consistent application of a soap containing a suitable antibacterial principle. This work furnishes the basis for the studies by Traub, Newhall and Fuller (133) on soaps containing as the antiseptic ingredient, 2,2'-dihydroxy-3,5,6-3', 5',6'-hexachlorodiphenylmethane, designated as G11. Soap of the proper basic composition containing two percent of G11 kills *S. aureus* at body temperature in a dilution of 1:20, in ten minutes, under the conditions of the F. D. A. testing procedure. (When tested as the monosodium or monopotassium salt, G11 is found to be strongly bacteriostatic for *S. aureus* and other gram-positive bacteria, but less active against the gram-negative microbes). However, Traub and coworkers showed that routine use of such a soap brings about a very sharp decline in the resident bacterial population as indicated by curve C in the following graph (Fig. VII).

Since the compound G11 is relatively non-toxic and free from any irritant or sensitizing action (134) when incorporated either in a soap (or in an ointment), there seems to be no objection to practicing continuous "degermation" of the skin through the routine use of a soap containing this anti-bacterial agent. Such a procedure should be of particular utility in connection with surgical scrub-up technique in that the scrubbing period could be materially reduced, with attendant benefits to the surgeon's hands, while the use of alcohol and iodine, etc. could be dispensed with altogether.

The capacity of lowering the resident bacterial population by means of a medicated soap is not limited to the compound G11, although most of the relevant work has been carried out with soap containing this chemical. Data are available which show that a similar effect can be obtained with soaps containing other phenol derivatives, singly or in combination, as antibacterial principle (135).*

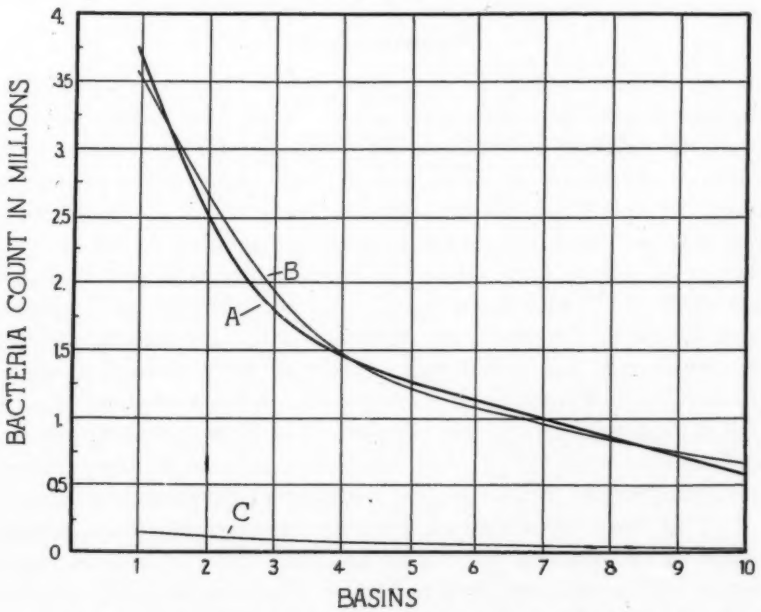
* For a discussion of "germicidal" soaps containing mercurials the paper by H. E. Morton (136) should be consulted.

Antifungal Agents

Fungi are simple plants which lack the ability of synthesizing their own food, and, therefore, must utilize a wide variety of organic materials for nutritive purposes. Mold, mildew and the various forms of rot and decay are associated with their biological activity; the first two represent aerial growth which, among other things, causes surface spotting, the latter two refer usually to sub-surface phenomena of spoilage or deterioration.

Fungus growths and their undesirable effects have been a problem for numerous branches of industry and agriculture. Much of the experience gained in the application of defensive measures has been transferred from the industrial and agricultural fields to that of the therapy of fungus diseases and related branches. The results of such

FIG. VII



A, Initial washings, control soap used in all basins. Average of 14 subjects. B, Control soap used in all basins. Average of 4 subjects who had used control soap for a period of 1 week. C, Control soap used in all basins. Average of 10 subjects who had used 2 per cent G-11 soap for a period of 1 week (Traub, Newhall and Fuller).

procedures "by analogy," had both favorable and unfavorable effects in their wake; since in the non-medical fields the solution of the fungus problem is sought in the eradication of the troublesome fungi, the direct application of the same principle in fungus infections at first suggested a somewhat indiscriminate use of chemicals with drastic action (usually formulations involving salicylic and benzoic acids; phenol, iodine, etc.). The result of this was an aggravation of the condition, caused by an extensive skin irritation, or a secondary bacterial infection originating in the area rendered susceptible by overtreatment (137). Because of this, emphasis is no longer being placed, in most cases, upon the need for a rapid access to the seat of the infection and the destruction of the fungus. The use of milder acting agents is being resorted to which through their fungistatic action tend to render the conditions unfavorable for the growth and activity of the fungus, and thus (aided by the host's own defensive mechanism) bring about an improvement or a cure.

Aliphatic Acids

In this connection, an important position has been assumed in the recent past by certain fatty acids. Their use appears to stem from the original observations by Peck and his coworkers (138, 139) on the action of sweat and its constituents upon pathogenic fungi. It was concluded that the fungistatic action of the perspiration was not due to its (normal) acidity, but rather to the presence therein of certain fatty acids. In support of this claim, Peck and coworkers studied the homologous series of aliphatic acids, beginning with formic and ending with capric acid, also the unsaturated undecylenic acid, and found that several of them showed a strong inhibitory action upon the *in vitro* growth of *Trichophyton gypseum*. Topical application in proper proportions of lactic, propionic, butyric and ascorbic acids (all of which are known to occur in perspiration), gave encouraging results in the treatment of fungous infections.

This work stimulated an extensive inquiry into the antifungal action of the different fatty acids and their salts, by Keeney, Sulzberger and others, and their respective collaborators (140, 141, 142, 143, 144, 145, 146).

Table XI illustrates the *in vitro* fungistatic action (upon *Trichophyton gypseum*) of some of the therapeutically more important aliphatic acids (in terms of their molar concentrations

x 10^3 at various pH, as observed by Foley and Lee (147). The highest activity is shown at pH 5. With the exception of propionic acid which is water soluble, higher fungistatic values are obtained when using a solubilizing agent, such as 50 percent propylene glycol; under these conditions, the fungistatic effectiveness is directly related to the length of the carbon chain. Similar findings were reported by Wyss, Ludwig and Joiner (148). Grunberg (149) studied the fungicidal (rather than the fungistatic) action of fatty acids at various pH levels, using a modification of Emmons' technique (150). He found that the fungicidal activity, too, increases with the chain length. Incidentally, there was no difference in the *in vitro* susceptibility between *Trichophyton gypseum* and *Trichophyton rubrum,* such as might have been expected from certain clinical findings.

A record of satisfactory clinical performance of formulations employing the different fatty acids has accumulated with respect

TABLE XI

FUNGISTATIC ACTION OF SEVERAL ALIPHATIC ACIDS ON *Trichophyton gypseum.*

AGENT	MOL. WT.	pH 5	pH 5.6	pH 7
Water Used as the Diluent				
Propionic	74	2.7	2.7	18.0
Heptylic	130	1.1	1.9	8.0
Caprylic	144	0.7	0.9	1.4
Pelargonic	158	2.1	2.6	20.0*
Capric	172	0.7	0.9	1.4
Undecylenic	184	0.6	0.9	1.3
Propylene Glycol Used as the Diluent				
Propionic		2.7	2.7	18
Heptylic		.51	.77	3.8
Caprylic		.14	.35	1.4
Pelargonic		.08	.42	2.6
Capric		.058	.23	.38
Undecylenic		.055	.136	.55

*More than.

to a number of conditions caused by fungi, such as *tinea pedis, tinea cruris, sycosis barbae,* etc.; infections caused by *Candida albicans* (otomycosis, mycotic vulvovaginitis, mycotic stomatitis, etc.) have also been treated successfully with formulations containing aliphatic fatty acids, singly or in combinations, including their sodium, calcium and zinc salts. In this connection, attention is called to the extensive report of findings on dermatophytoses by Hopkins, Fisher, Hillegas, Ledin, Rebell and Camp (151). A summary of results with anti-fungal ointment widely used by the U. S. Army was rendered by Sullivan and Fishbein (152). This ointment contains undecylenic acid; its action was compared with that of two proprietary ointments containing respectively undecylenic acid plus zinc undecylenate, and propionic acid plus sodium propionate. The undecylenic acid-zinc undecylenate combination was found to be the most effective of all three, the zinc salt evidently enhancing the action of the acid. Incidentally, it may be of interest that in 81 percent of all cases the causative fungus was *Trichophyton gypseum.*

Keeney, Ajello, Lankford and Lankford (144) claim that sodium caprylate is superior to the propionic acid-sodium propionate or to the undecylenic acid-zinc undecylenate combination (153). An ointment containing 10 percent of sodium caprylate is not only strongly antifungal, but its bacteriostatic effect upon *S. aureus* compares with that of a 10 percent ammoniated mercury ointment. In fact, Keeney and coworkers consider sodium caprylate superior to any other known preparation for the treatment of dermatomycosis of the feet. A drug combining the propionate and caprylate principles has also been developed. It is claimed that this combination yields a better fungistatic effect than produced by either agent alone.

Propylene glycol dipropionate seems to be the first fatty acid ester to be tested for antifungal action. Bereston (154), who used it successfully, attributes its effectiveness to its capacity of interfering with the fat metabolism of fungi.

Phenolic Fungicides and Fungistats

As to antifungal agents other than the aliphatic acids, their salts and derivaties, the report by Hopkins and collaborators refers to dinitro-cyclohexylphenol which gave as a high a percentage of satisfactory results as did undecylenic acid. Of course, phenolic compounds (including phenol, cresol, the alkyl, aryl and alkaryl

derivatives of phenol, cresol and xylenol, as well as their respective halogenation and nitration products) are being used extensively in industrial fungus prevention. Some of them are very potent; their therapeutic use must be approached with great caution since, according to Hopkins and collaborators, powerful fungicides rarely accelerate the cure, but frequently cause severe irritation. The use of saponated cresol solution was recommended by Peck and Schwartz (155). Foley and Lee (147), in their recent work on trimethylcetylammonium pentachlorophenate attempted to combine the well known antifungal effects of a cationic agent and of a polyhalogen phenol derivative; some promising results *in vitro* were obtained. McKee, Herrmann and Karp (156) used this product with considerable success in the treatment of *tinea tonsurans*. Weidman and Glass (157) reported favorably upon the use of metacresylacetate (Cresatin-Sulzberger) in the treatment of dermatophytosis of feet. Incidentally they did not find the lesions caused by *Trichophyton purpureum* more resistant to treatment than those produced by other fungi.

Other Antifungal Drugs

Copper salts are used industrially for their fungicidal action. It is not surprising, therefore, that copper undecylenate, combining the antifungal effects of copper and of undecylenic acid, was among the most effective medications used in treating an epidemic of ringworm of the scalp caused by *Microsporon audouini* (158). An equally effective medication was supplied by salicylanilide also "borrowed" from the industrial field where it is used among other things in the protection of woolens against mildew during shipment.

An example of "exchange of information" between the agricultural and medical fields is furnished by Kligman's and Rosenzweig's work on dithiocarbamates (159). This class of compounds was studied previously by several investigators for its capacity of controlling fungous diseases of tomatoes, potatoes, beans, etc. Table XII shows that among the several dithiocarbamates tested there are not only some powerfuly fungistatic representatives such as disodium ethylene bisdithiocarbamate or calcium dimethyl-dithiocarbamote, but also that these compounds suffer hardly any impairment of their anti-fungal action in the presence of 20 percent of blood (Table XIII). Moreover, these compounds are bacterio-

TABLE XII

FUNGISTATIC ACTION OF DITHIOCARBAMATE DERIVATIVES (KLIGMAN AND ROSENZWEIG)

Compound	Paper Disk Method Millimeters of Inhibition								Dilution Method Minimal Fungistatic Concentration (%)		
	Trichophyton mentagrophytes				Microsporum lanosum						
	1:1,000	1:5,000	1:10,000	1:50,000	1:1,000	1:5,000	1:10,000	1:50,000	Micro-Sporum audouini	Trichophyton purpurum	Epidermophyton floccosum
Sodium dimethyldithiocarbamate	30	24	20	0	35	28	22	17	0.02	0.01	0.1
Calcium dimethyldithiocarbamate	45	28	23	21	49	43	31	24	0.02	0.002	0.01
Ferric dimethyldithiocarbamate	35	25	23	18	38	26	23	17	0.01	0.01	0.01
Zinc dimethyldithiocarbamate	31	24	18	0	37	31	20	15	0.02	0.01	0.01
Disodium ethylene bisdithiocarbamate	68	55	48	32	56	44	38	33	0.02	0.01	0.01
Ethyl carbamate (1)	0	0	0	0	0	0	0	0	—	—	—

TABLE XIII

EFFECT OF WHOLE BLOOD ON THE FUNGISTATIC ACTION OF DITHIOCARBAMATES (ON *Torula histolytica*) (KLIGMAN AND ROSENZWEIG)

Compound	Pennsylvania Medium				20% Blood Medium			
	1:1,000	1:5,000	1:10,000	1:50,000	1:1,000	1:5,000	1:10,000	1:50,000
Sodium dimethyldithiocarbamate (1)	30	19	18	14	25	13	13	0
Calcium dimethyldithiocarbamate (2)	51	38	35	22	30	28	22	18
Iron dimethyldithiocarbamate (3)	42	28	24	18	40	17	15	13
Zinc dimethyldithiocarbamate (4)	38	33	20	18	28	18	15	13
Disodium ethylene bisdithiocarbamate (5)	55	46	38	34	51	35	27	23

static especially with respect to gram-positive bacteria; thus disodium ethylene bisdithiocarbamate inhibits the growth of *S. aureus* in a dilution of 1:100,000. (The corresponding dilutions with respect to the gram-negative *E. typhosa* and *E. coli* are respectively 1:5000 and 1:10,000). Their toxicity is low. With properties such as these a favorable clinical trial might be anticipated.

A series of naphthoquinones and their various derivatives (including 2-methyl-1,4-naphthoquinone or Vitamin K) was also studied by Kligman and Rosenzweig *in vitro,* but with more indifferent results. However, phenanthraquinone-9,10 appears to offer some possibilities despite the reduction of its fungistatic action in the presence of whole blood. Prior to this, Vinet (160) reported upon the antifungal (and antibacterial) action of a series of substituted naphthoquinones among which 2-chloronaphthoquinone was found to be particularly effective as a fungistat.

Notes on Testing Methods

When inquiring into the fungicidal or fungistatic action of a given chemical, or of a combination of chemicals, one should keep the distinction between the following two different purposes in mind: Is the anti-fungal agent to be used mostly on inanimate objects in order to free them from the presence of pathogenic fungi, or is it being considered for use on the body in order to combat a fungous infection and its sequelae? It is obvious that the same criteria of usefulness cannot be applied to both these purposes, and this is why this distinction should be reflected in the testing methods, allowing for some areas of overlapping where justified logically.

As in the case of disinfectants and antiseptics, so also here a testing method should attempt to reproduce practical conditions as closely as possible, allowing, in addition for an adequate margin of safety. With respect to the fungicidal action of the "disinfectant" category, the method by Emmons (150) can be used which employs a particular strain of *Trichophyton mentagrophytes* (synonymous with *Trichophyton gypseum* and *Trichophyton interdigitale*) as test organism; the standard resistance of this strain is verified by means of phenol acting upon a suspension of a definite number of spores. The testing procedure itself resembles that of testing disinfectants by the F. D. A. method, and to this extent it reflects the technique developed by Klarmann, Shternov and Costigan (161). The latter

method uses, as principal test organism, a strain obtained from and identified by Osborne and Hitchcock as *Trichophyton rosaceum* (162) although it also provides for the use of *Trichophyton gypseum.* As to the former, Emmons claims that the strain used is a saprophytic fusarium; be that as it may, this organism lends itself well to standardization, and its resistance to phenol is reproducible regardless of the number of transfers. This resistance compares favorably with that of the resistant strains of *Trichophyton mentagrophytes.* There are some indications to the effect that the latter organism is subject to variations in strain resistance which would tend to cause some difficulty in a test patterned along the lines of the F. D. A. procedure.

As to *in vitro* tests of antifungal agents for therapeutic use, a number of testing methods have been suggested. Among the more recent ones is Sharlit's (163) "membrane method," which depends upon the migration of the fungistatic or fungicidal agent, out of a collodion membrane lining the culture tube, into the culture. The method of Burlingame and Reddish (164) employs pieces of agar inoculated with pathogenic fungus cultures which are exposed to the action of the solution under test for definite periods of time, washed in broth, spread over sterile slants of Sabouraud's agar and incubated for evidence of growth. Among other things, this procedure is intended to supply some information as to the penetrating properties of the anti-fungal agents tested. A somewhat similar method has been described by Rose and Miller (165).

Since one of the requirements of clinical usefulness appears to be satisfied by the evidence of fungistatic action, i. e., without demanding one of fungicidal potency, the simple disc method proposed by Kligman and Rosenzweig merits consideration (166). While methods embodying the same principle have been used before, these investigators, without claiming originality for their procedure, perfected and standardized it with respect to its several features. The method calls for the placement of filter paper discs saturated with the fungistatic material, upon the surface of agar plates infected with one of several varieties of fungi, and the observation or measurement of the zones of inhibition following incubation for a time period which varies with the individual test organisms. The method lends itself for use with both soluble and insoluble materials.

REFERENCES (Continued)

(114) Dodd, M. C., and Stillman, W. B.: *J. Pharmacol. Exp. Ther., 82*:11 (1944).

(115) Shipley, E. R., and Dodd, M. C.: *Surg. Gyn. Obst., 84*:366 (1947).

(116) Cramer, D. L., and Dodd, M. C.: *J. Bact., 51*:293 (1946).

(117) Dodd, M. C., Hartman, F. W., and Ward, W. C.: *Surg. Gyn. Obst., 83*:73 (1946).

(118) Downing, J. G., Hanson, M. C., and Lamb, M.: *J. A. M. A., 133*:299 (1947).

(119) Bliss, E. A., and Deitz, H. C.: *Bull. Johns Hopkins Hosp., 75*:1 (1944).

(120) Hartmann, F. W.: *J. Bact., 47*:259 (1944).

(121) Fleming, A.: Chemistry and Industry, Jan. 20, 1945, p. 18.

(122) Gulland, J. M., and Farrar, W. V.: *Ann. farm. bioguim. (Argentina), 15*:73 (1944).

(123) Fleming, A.: *J. Exp. Pathol., 1*:274 (1926).

(124) Nye, R. N.: *J. A. M. A., 108*:280 (1937).

(125) Welch, H., and Brewer, C. M.: *Amer. J. Publ. Health, 32*:261 (1942).

(126) Welch, H., Slocum, G. G., and Hunter, A. C.: *J. Lab. Clin. Med., 27*:1432 (1942).

(127) Klarmann, E. G.: *Soap and Sanit. Chem.,* Dec. 1933.

(128) Klarmann, E. G., and Shternov, V. E.: *Soap and San. Chem. J.,* 1941.

(129) Walker, J. E.: *J. Inf. Dis., 35*:556 (1924); *37*:181 (1925); *38*:127 (1926).

(130) Stuart, L. S., and Pohle, W. D.: *Soap and Sanit. Chem., 17* (2), *34* (3), *34* (1941).

(131) Pohle, W. D., and Stuart, L. S.: *Oil and Soap, 18*:2 (1941).

(132) Price, J.: *Arch. Surg., 38*:528 (1939); *J. Inf. Dis., 63*:301 (1938).

(133) Traub, E. F., Newhall, C. A., and Fuller, J. R.: *Surg. Gyn. Obst., 79*:205 (1945).

(134) Udinsky, H.: *J. Med. Soc., N. J., 42*:I, 15 (1945).

(135) Klarmann, E. G., Wright, E. S., and Gates, L. W.: Unpublished data.

(136) Morton, H. E.: *J. A. M. A., 124*:1195 (1944).

(137) Weidman, F. G., Emmons, C. W., Hopkins, J. G., and Lewis, G. M.: *J. A. M. A., 128*:805 (1945).

(138) Peck, S. M., and Rosenfeld, H.: *J. Investig. Dermatol., 1*:237 (1938).

(139) Peck, S. M., Rosenfeld, H., Leifer, W., and Bierman, W.: *Arch. Dermatol. Syphilol., 39*:126 (1939).

(140) Keeney, E. L.: *Bull. Johns Hopkins Hosp., 73*:479 (1943).

(141) Keeney, E. L., and Broyles, E. N.: *Bull. Johns Hopkins Hosp., 73*:479 (1943).

(142) Keeney, E. L., Ajello, L., and Lankford, E.: *Bull. Johns Hopkins Hosp., 75*:377 (1944).

(143) Keeney, E. L., Ajello, L., Broyles, E. N., and Lankford, E.: *Bull. Johns Hopkins Hosp. 73*:417 (1944).

(144) Keeney, E. L., Ajello, L., Lankford, E., and Lankford, M. L.: *Bull. Johns Hopkins Hosp., 77*:422 (1945).

(145) Sulzberger, M. B., Shaw, H. C., and Kanof, A.: *U. S. Nav. Med. Bull., 45*:237 (1945).

(146) Sulzberger, M. B., and Kanof, A.: *Arch. Dermatol. Syphilol., 55*:391 (1947).

(147) Foley, E. J., and Lee, S. W.: *J. Investig. Dermatol., 10*:249 (1948); *8*:1 (1947).

(148) Wyss, O., Ludwig, B. J., and Joiner, R. R.: *Arch. Biochem., 7*:415 (1947).

(149) Grunberg, E.: 47th General Meeting S. A. B., May, 1947.

(150) Emmons, C. W.: *Amer. J. Publ. Health, 35*:839 (1945).

(151) Hopkins, J. G., Fisher, J. K., Killegas, A. B., Ledin, B., Rebell, G. C., and Camp, E.: *J. Investig. Dermatol., 7*:239 (1946).

(152) Sullivan, M., and Fishbein, H. A.: *J. Investig. Dermatol., 10*:293 (1948).

(153) Shapiro, A. L., and Rothman, S.: *Arch. Dermatol. Syphilol., 53*:166 (1945).

(154) Bereston, E. S.: *J. Investig. Dermatol., 8*:227 (1947).

(155) Peck, S. M., and Schwartz, L.: *Publ. Health Reports, 58*:(9) 337 (1943).

(156) MacKee, G. M., Hermann, F., and Karp, F.: *J. Investig. Dermatol., 7*:43 (1946).

(157) Weidman, F. D., and Glass, F. A.: *Arch. Dermatol. Syphilol., 53*:213 (1946).

(158) Schwartz, L., Peck, S. M., Botvinick, I., and Leibovitz, A. L.: *Publ. Health Bull.,* No. 294 (1946).

(159) Kligman, A. M., and Rosenzweig, W.: *J. Investig. Dermatol., 10*:59 (1948).

(160) Vinet, A.: *C. r. soc. biol., 139*:155 (1945).

(161) Klarmann, E. G., Sternov, V. A., and Costigan, S. M.: *J. Bact., 42*:225 (1941).

(162) Osborne, E. D., and Hitchcock, B. S.: *J. A. M. A., 97*:453 (1931).

(163) Sharlit, H.: *Arch. Dermatol. Syphilol., 31*:217 (1935).

(164) Burlingame, E. M., and Reddish, G.: *J. Bact., 38*:525 (1939).

(165) Rose, S. B., and Miller, R. E.: *J. Bact., 38*:525 (1939).

(166) Kligman, A. M., and Rosenzweig, W.: *J. Investig. Dermatol., 10*:51 (1948).

(167) Flett, L. H., Haring, L. C., Guiteras, L. F., and Shapiro, R. L.: *J. Bact., 50*:591 (1945).

(168) Mallmann, W. L., Leavitt, A., and Joslyn, D. A.: *Proc. Soc. Exp. Biol. Med., 68*:401 (1948).

THE EFFECT OF WATER ON THE EFFICIENCY OF ANTISEPTICS IN W/O EMULSIONS[1]

By Alfred Halpern, Ph. D.* and Lois M. Hartwell, B. S.**

THE subject of hydrophilic ointments has received much attention in recent years, culminating in the inclusion of a hydrophilic ointment in the U. S. P. XIII. The presence of water in an ointment base was shown to be desirable by many investigators (1-4). An O/W emulsion base was claimed to be superior to the W/O type (5,6) for use as a vehicle for antiseptics, although Wimmer and Strakosch (7) and Kuney (8) reported good results with the latter type bases. It was also shown by some investigators (9,10) that water was not a necessary ingredient for the production of antiseptic ity in ointments.

Busse (11) and Neuroth and Lee (12) reviewing the different ointment bases came to the conclusions that there was no universal ointment base and that claims for the water-containing bases have not been fully justified.

For the most part, the various studies of the antiseptics in ointment bases were conducted with preparations containing a fixed quantity of water. No study of a possible optimum concentration of water in these bases was made. In the course of a study of the hydrophilic properties of ointment base constituents (13-15) it was shown that varying amounts of water up to 1500% could be incorporated in petrolatum. It was of interest to determine the effect of increasing amounts of water on the antiseptic activity of various agents and as a complementary phase, compare the activity of the different emulsifying agents on the antiseptic activity of the test compounds. This study was limited to the water in oil emulsions.

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Experimental

The vehicles used in this study are not ointment bases. They are merely mixtures of the emulsifying agent, petrolatum, water, and the test compound. For the most part these simple mixtures were not stable for any great length of time and were freshly prepared before testing. The simple mixtures were used in order to best evaluate the effects of the individual components.

The preparations were made in the usual manner and the indicated quantity of antiseptic agent incorporated by levigation. In the cases of phenol, and cetyl pyridinium chloride, the agent was dissolved in the aqueous phase prior to emulsion formation.

Method of Evaluating Antiseptic Activity

A culture of Staphylococcus aureus Rosenbach (#209) especially for disinfectant testing was procured from the American Type Culture Collection. It was placed on agar prepared according to the specifications of the Food and Drug Administration (16) and transferred daily in broth of the same composition.

Prior to the preparation of the agar test plates, the strength of the broth culture to be used was determined against phenol according to F. D. A. directions. A 1:60 solution of phenol killed the organism in 10 min., but not in 5 min. at 20° C. A 1:70 solution of phenol did not kill the organism in 5, 10, or 15, min.

Agar test plates were prepared each containing 0.1 cc. of a 24 hour broth culture to 20 cc. of F. D. A. agar. The sample of ointment to be tested was shaped into a flat pancake 1.5 cm. in diameter and 0.4 cm. thick, with the aid of sterile spatulas, and placed in intimate contact with the agar surface. The plates were incubated in an inverted position at 37.5° C. for 24 hours. At the end of this time, the width of the zone of inhibition was measured in several places and an average taken, which was then recorded. All samples were tested in duplicate. Pieces of the zones of inhibition were transferred to F. D. A. broth for confirmation of bactericidal or bacteriostatic activity. No growth was observed in these sub-cultures except those from phenol and sulfathiazole, whose zones of inhibition were not clear. The results of the bacteriological evaluation are noted in table I.

TABLE I

The Effect of Water on the Antiseptic Activity in W/O Emulsions

% Emulsifying Agent in Petrolatum	% Water	Zone of Inhibition in mm. 10% NH_2HgCl	10% HgCl	10% HgO	2% Phenol	5% I_2	10% Sulfathiazole	10% H_3BO_3	Cetyl Pyrid Chlor. (a) (1%)
Cetyl Alcohol	0	2.5	2	4	0	7	0	0	0
4%	10	3.5	3	4	0	7	0	0	0.5
	20	4.5	3	4	0	7	0	0	0.5
	30	4.5	1	4	0	8	0	0	1.0
	38	5.0	1	4	0	8	0	0	2.0
Stearyl Alcohol (b)	0	2	1	3	0	6	0	0	0
6%	10	3	3	4	0	6	0	0	0.5
	20	3	3	4	0	7	0	0	1
	30	4	3	4	0	8	0	0	1
	35	4	3	4	0	8	0	0	2.5
	40	4	3	4	0	8	0	1	2.5
	45	4	1	4	0	8	1	1	2.5
Eicosyl Alcohol (a)	0	2	2	3	0	7	0	0	0.5
5%	10	3	3	3	0	7	0	0	0.5
	20	3	3	3	0	7	0	0	2.0
	30	5	1	3	0	7	0	0	2.0
	40	5	1	4	0	7	0	1	3.0
	50	5	1	4	0	7	0	1	3.0

Docosyl Alcohol (b)	0	2	2	3	0	8	0	0	0.5
4%	10	2	3	3	0	8	0	0	1.0
	20	2.5	3	3	0	8	0	0	1.0
	30	2.5	3	4	0	8	0	0	2.5
	40	4	3	4	0	8	0	0	2.5
Triacontanol (a)	0	2	3	3	0	8	0	0	0
3%	10	2	3	3	0	8	0	0	0.5
	20	4	3	3	0	7	0	0	0.5
	30	4	1	4	0	7	0	0	1.5
Glycerol Mono-Oleate (a)	0	2	2	5	0	10	0	0	0
10%	10	3	2	5	0	10	0	0	0
	20	3	2	5	0	10	0	0	0.5
	30	3	2	5	0	10	0	0	0.5
	40	5	3	6	0	10	1	0	1.5
	50	6	3	6	0	12	1	0	2
	60	6	3	6	0	12	2	1	2
Sorbitan Mono-Laurate (c)	0	3	2	5	0	8	0	0	0
10%	10	3	2	5	0	8	0	0	0
	20	3	2	5	0	8	0	0	0
	30	5	2	5	0	10	0	0	0.5
	40	5	2	5	0	12	0	0	1
	50	5	2	5	0	12	0	0	1
	60	5	2	5	0	12	1	1	1

TABLE I (Continued)

% Emulsifying Agent in Petrolatum	% Water	10% NH_2HgCl	10% HgCl	10% HgO	2% Phenol	5% I_2	10% Sulfathiazole	10% H_3BO_3	Cetyl Pyrid Chlor. (a) (1%)
		Zone of Inhibition in mm.							
Sorbitan Mono-Palmitate (c)	0	3	2	5	0	10	0	0	0
10%	25	3	2	5	0	10	0	0	0
	45	3	2	5	0	10	0	0	0
	60	4	3	6	0	12	0	0	0.5
	75	4	3	6	0	12	1	2	1
	100	5	4	6	0	12	2	2	1
	150	6	4	6	0	12	2.5	2	2.5
15%	200	6	4	6	0	12	2.5	2	2.5
Sorbitan Mono-Stearate (c)	0	2	3	6	0	12	0	0	0.5
10%	25	3	3	6	0	12	0	0	0.5
	50	3	4	6	0	12	1	0	0.5
	100	5	4	6	0	12	1	1	1
	150	5	4	6	0	14	1	1	1
	200	5	4	6	0	14	2	2	1
	300	5	4	6	0	14	2.5	2	2.5
	400	5	4	6	0	14	2.5	2	2.5

Sorbitan Mono-Oleate (c)	0	3	3	6	0	10	0	0	1
10%	50	3.5	4	6	0	10	0	0	1
	100	3	4	6	0	11	1	2	2
	200	5	5	6	0	11	1	2	2
	300	5	5	6	0	12	2	2	3
	500	7	5	6	0	14	2	2	3
	750	7	5	7	1	14	2	2	4
	1000	7	7	7	1	15	2.5	3	4.5
15%	1250	7	7	6	2	15	2.5	3	4.5
	1400	7	7	6	2	15	3	3	4.5
Sorbitan Sesqui-Oleate (c)	0	2	3	6	0	10	0	0	0
10%	50	3	3	6	0	10	0	0	0
	100	3	4	6	0	12	1	0	1
	200	5	4	6	0	12	1	1	1
	300	4	4	5	0	12	2	1	2.5
	400	4	4	5	0	12	2	1	2.5
	500	5	5	5	0	12	2.5	1	3
Sorbitan Sesqui-Oleate	750	5	5	5	1	12	2.5	1	3
(c) (Cont.)	1000	7	7	5	1	12	2.5	2	3
15%	1250	7	7	6	2	14	3	2	3
	1400	7	7	6	2	14	3	2	3

TABLE I (Continued)

% Emulsifying Agent in Petrolatum	Zone of Inhibition in mm.								
	% Water	10% NH_2HgCl	10% HgCl	10% HgO	2% Phenol	5% I_2	10% Sulfathiazole	10% H_3BO_3	Cetyl Pyrid Chlor. (a) (1%)
Sorbitan Di-Oleate (c) 10%	0	3	3	4	0	10	0	0	0.5
	50	3	3	4	0	10	0	0	0.5
	100	3	3	5	0	10	1	0	1.5
	200	5	3	5	0	12	1	0	1.5
	300	5	3	6	0	12	1	0	2
	400	5	4	6	0	13	1	1	2
	500	5	4	6	0	13	2	1	2.5
	750	6	4	6	0	13	2	1	3
	1000	6	4	6	0	14	2.5	1	3
Mannitan Oleate (c) 10%	0	1	3	5	0	8	0	0	0.5
	50	3	3	5	0	12	0	0	0.5
	100	3	3	5	0	12	1.5	0	1.5
	250	3	3	5	0	12	1.5	0	1.5
	500	5	3	5	0	12	1.5	1	2
	750	5	5	5	2	12	2.5	1	2.5
	1000	5	5	5	2	15	2.5	1	2.5

Mannide Oleate (c)	0	2	3	5	0	10	0	0	0
10%	100	2	3	5	0	10	1	0	1
	200	3	3	4	0	10	1	0	1
	300	4	3	5	0	10	1	0	2
	400	5	5	5	0	10	1	0	2
	500	5	5	5	0	10	2	1	3
	750	5	5	5	1	10	2	1	3.5
Wool Fat (10%)	0	5	3	6	0	15	0	0	0.5
	10	6	3	6	0	15	0	0	1
	25	6	3	6	0	15	0	0	1
	40	6	3	6	0	15	1	0	2

(a) Prepared in our laboratories.

(b) Samples were furnished us by E. I. duPont de Nemours & Co., Wilmington, Delaware, through the courtesy of Dr. J. H. Shipp.

(c) Furnished us by the Atlas Powder Co., Wilmington, Delaware, through the courtesy of Mr. William G. Griffin of the Central Research Laboratory. These products are commercially available under the registered trade marks of ARLACEL, TWEEN, and SPAN.

Discussion

Our results indicated that water was not a necessary ingredient for the production of antisepticity in ointments with certain ingredients. The degree of antiseptic action produced, however, was influenced by the amount of water present in the mixture. With the exception of calomel, the antiseptics studied evidenced an increased effect with the increase in the water content of the base. Calomel showed a decrease in activity with the greater water content only in those mixtures emulsified with the fatty alcohols. This type of response was not evidenced with the fatty acid esters of sorbitan and mannitan and the glyceryl monooleate emulsions. Sulfathiazole and phenol showed consistently poor results.

The differences in the activity of the various antiseptic agents in the mixtures containing no water, serves best to evaluate the effect of the emulsifying agents on antiseptic activity. The effects noted presumably were due to the different surface tension reducing properties of the individual agents and their resultant effect on the release of the drug from the mixture. The fatty acid esters of sorbitan and mannitan exerted a greater effect than the fatty alcohols, which is in agreement with the reported emulsifying efficiencies for these compounds (13-15).

Generally our results are in accord with those reported by Foley and Lee (1), Bandelin and Kemp (17), and Hart and Huyck (10) in studies made with the same or similar type antiseptics using W/O emulsion bases. Iodine is a consistently good antiseptic in this type of an emulsion base, and while the mercurials evidence some activity in the W/O base, it is not as good as that shown by the O/W bases (1).

It was pointed out that the agar plate method was not an adequate measure of the antiseptic activity, but rather determined the diffusion coefficient through the agar gel (10). This technique however has been so widely used that it was felt to be of value as a basis of comparision. The conclusions of Foley and Lee (1) that the antiseptic properties of the chemical or medicament has as much or perhaps more to do with the bacteriostatic action of the product than does the composition of the vehicle in which it has been incorporated appears to be well founded.

Summary

The effect of varying concentrations of water in W/O emulsions on antiseptic activity was determined. Water is not a necessary ingredient for the production of antisepticity in an ointment although the degree of antiseptic action is influenced by the quantity of water present. The properties of the antiseptic agent is a prime factor in its efficiency in an ointment base.

BIBLIOGRAPHY

(1) Foley, E., and Lee, C. O.: *J. Am. Phar. Assoc., 31*:105 (1942).

(2) Reddish, G. F., and Wales, H. W.: *J. Am. Phar. Assoc., 18*:576 (1929).

(3) Wood, W. C.: *Pharm. J., 142*:327 (1939).

(4) Gershenfeld, L., and Brillhart, R. E.: *This Journal, 111*:430 (1939).

(5) Gibson, A. J., Parker, H. E., and Almus, A.: *J. Am. Phar. Assoc., 30*:196 (1941).

(6) Fischler, F.: *Pharm. Zentralhalle, 74*:221 (1933).

(7) Wimmer, L. H., and Strakosch, E. A.: *J. Am. Med. Assoc., 118*:22 (1942).

(8) Kuney, E. L., Pembroke, R. H., Chatard, F. E., and Ziegler, J. M.: *J. Am. Med. Assoc., 117*:415 (1941).

(9) Husa, W. J., and Radin, J. M.: *J. Am. Phar. Assoc., 21*:861 (1932).

(10) Hart, F., and Huyck, C. L.: *J. Am. Phar. Assoc., 21*:861 (1932).

(11) Busse, L. W.: *J. Am. Phar. Assoc. Pract. Phar. Ed., 4*:314 (1943).

(12) Neuroth, M. L., and Lee, C. O.: *J. Am. Phar. Assoc. Pract. Phar. Ed., 6*:285 (1945).

(13) Halpern, A., and Zopf, L. C.: *J. Am. Phar. Assoc., 36*:101 (1947).

(14) Halpern, A., and Wilkins, W.: Presented to the Scientific Section A. Ph. A., San Francisco, Calif., August, 1948.

(15) Halpern, A., and Squeglia, N.: Presented to the Scientific Section A. Ph. A., San Francisco, Calif., August, 1948.

(16) Ruehle, G. L. A., and Brewer, C. M.: *U. S. Dept. of Agric.*, Circ. No. 198 (1931).

(17) Bandelin, F. J., and Kemp, C. R.: *J. Am. Phar. Assoc., 35*:65 (1946).

SELECTED ABSTRACTS

Diphtheria Immunization With Precipitated Pertussis Vaccine and Diphtheria Toxoid. J. A. Bell. *J. A. M. A. 137:*1009 (1948). A carefully controlled study of the immunizing value in young children of a mixture of alum-precipitated diphtheria toxoid and alum-precipitated pertussis vaccine as compared with an unmixed alum-precipitated diphtheria toxoid is described by the author. It had been previously shown that an admixture of the toxoid and the vaccine does not impair the antigenic potency of either product.

The mixed product was prepared from 2 parts of diphtheria toxoid and 1 part of a suspension of 30,000,000,000 phase I *Hemophilus pertussis.* The unmixed product was prepared from 2 parts of the same lot of the toxoid and 1 part of isotonic solution of sodium chloride.

Children who received two doses, four weeks apart, of the unmixed preparation had 3 times as many failures to immunize against diphtheria as the children who received two doses of the mixed product. The two-dose schedule was 3 times as effective as the one-dose schedule, whichever product was used. There were twice as many failures to immunize against diphtheria when both doses were given at 2 to 5 months of age than when at least one of the doses was given at 6 to 23 months of age. This held true for either product. The Schick test, performed one year after immunization, was the index of diphtheria immunity. Of the 1,025 children who were Schick tested after having received one or two doses of the mixed or the unmixed preparations 90.6 per cent were found to be immune. Only 82.3 per cent of the 707 mothers tested were found to be immune.

From these results it was felt that the over-all effort to immunize at an early age was highly successful. Although children 2 to 5 months of age were not immunized as readily as those 6 to 23 months of age, the mixed product was sufficiently superior to the unmixed preparation that it appeared to be a better immunizing agent among the younger group than did the unmixed product at any age.

Stimulation of Gastric Secretion by Caffeine. D. R. Wood. *Brit. Med. J.* No. 4570:283 (1948). Previous studies had shown that doses in the vicinity of 125 mg. of caffeine will cause an increase in the secretion of acid gastric juice in cats. Other animals are likewise affected and man seemed to be particularly susceptible.

The author reports the results of a study to determine the effects of small doses of caffeine, which did not increase gastric secretion themselves, upon the gastric stimulation of histamine. The cat was used as the experimental animal. Doses of caffeine were 10 to 20 mg. per Kg. of body weight. Theobromine and theophylline were also compared with caffeine. It was found that following an injection of caffeine the gastric stimulation effect of histamine was greatly potentiated. The potentiation was not as great nor as consistent following injections of theobromine or theophylline.

The gastric mucosa of the cats were observed after the experiments were completed. There was hyperaemia and engorgement of the mucosa particularly marked after caffeine administration, but to some extent after the other xanthine derivatives. No such effects were observed after histamine alone.

The author concludes that the vascular and cellular changes which are produced by caffeine may make the mucosa more susceptible to the proteolytic action of acid and pepsin secretion. Thus caffeine may be a factor in the formation or perpetuation of peptic ulcers. Although these experiments were performed on cats and it is not yet certain as to the effect of caffeine on the mucosa of human beings, the results seem to verify the conclusion that ulcer patients should markedly restrict their intake of caffeine-containing beverages.

Streptomycin in the Treatment of Tuberculosis of Bones and Joints. W. H. Bickel, H. H. Young, K. H. Pfuetze, and T. Norley. *J. A. M. A. 137*:682 (1948). Experience in the use of streptomycin for the treatment of tuberculosis in 16 patients having 19 involved joints is reported by the authors. Tuberculous sinuses were present in 4 of the patients.

Streptomycin was administered in daily doses varying between 0.75 Gm. and 2 Gm. During the early part of the study the anti-

biotic was given intramuscularly in 2 to 6 cc. of isotonic solution of sodium chloride at intervals of four hours. During the latter portion of the study the daily dose was divided in half and given in 5 cc. of the same vehicle. The period of treatment varied from 66 days to 190 days with an average of 112 days. The average total dosage of streptomycin during the treatment period was 134 Gm. As a result of the experience gained the authors conclude that 1 Gm. of streptomycin daily for a period of 90 days should be a satisfactory course of treatment.

Mild toxic symptoms were noted in 9 of the 16 patients. The most prominent symptoms were dizziness and objective staggering. In one patient urticaria, fever, and vomiting following 7 days of 2 Gm. a day made it necessary to discontinue the drug. However, a desensitizing course made it possible to reinstitute therapy for a complete course. Deafness was not encountered in any patient. The authors point out that maintaining the dose of streptomycin at 1 Gm. a day greatly reduced the incidence of toxic reactions.

The authors considered response to this therapy with streptomycin as favorable in 9 cases, fair in 1 case, no benefit in 4 cases, and too early in the treatment to evaluate in 2 cases. In view of the great difficulty previously encountered in the treatment of tuberculosis of the bone and joint the results of this preliminary study may be considered as encouraging.

Antiulcer Vitamin Indicated by Research. Garnett Chaney. *Chem. and Eng. News 26:*2218 (1948). The inhibition of peptic ulcers in guinea pigs has been attributed to an unidentified vitamin U. Research conducted with guinea pigs at the Stanford University School of Medicine has been so favorable that carefully controlled diet studies of human ulcer patients are considered as warranted. However, it is not yet known whether or not the human stomach behaves just as does the stomach of the guinea pig.

This antiulcer factor is found in such foods as alfalfa, kale, lettuce, other fresh greens, cereal grasses, fresh milk, raw egg yolks, wheat bran, soybean oil, olive oil, and liver fat. The vitamin is ap-

parently very sensitive to heat. With one group of guinea pigs the diet was made deficient in the vitamin by heating it. Another group of animals was given the same diet, unheated, with liberal supplements of foods containing the antiulcer factor. As a result of this diet it was found that 87.5 per cent of the guinea pigs receiving the heated diet developed ulcer lesions, but none of the guinea pigs receiving the unheated, supplemented diet had ulcer lesions.

As an additional test of the effect of heat on the factor, two groups of guinea pigs were fed the very same diet, except that the food of one group was heated and the other was not. As a result of these diets 90 per cent of the animals receiving the heated food developed ulcers but only 25 per cent of those receiving the unheated food developed ulcers.

As a result of these observations the author raises the question as to whether or not the present high incidence of peptic ulcers in human patients may be due, at least in part, to the lack of raw food in the average diet.

A Clinical Study of Globin Insulin. G. M. Wauchope. *Brit. Med J.* No. 4568:191 (1948). Globin insulin (G. I.) is a slow-acting insulin intermediate in duration of action between protamine-zinc insulin (P. Z. I.) and soluble insulin (S. I.). From the aspect of the patient it has the advantage of simplicity.

The survey reported by the author is based upon 366 ambulatory patients who had been taking G. I. for one to four years. The patients vary in age from about 2½ to over 65 years. The majority of the patients of all ages, actually 73 per cent, were taking less than 40 units. One patient required as high as 176 units. Previously it had been reported that G. I. was satisfactory for patients on small or moderate doses but unsatisfactory when high doses were required. However, Wauchope found that patients on large doses of G. I. do as well as those on smaller doses. Clinically there was no difference and the patients requiring the high doses were not subject to reactions.

Among 150 patients whose records were complete over several years, 40 reported reactions to G. I. Those who had reactions usually

had many over the years but only 3 of all those reporting reactions were severe. The incidence of reactions to G. I. was less than with P. Z. I. and S. I. There was no relation between the age nor the size of the dose and the incidence of reactions.

Although it is difficult to demonstrate the success or failure of insulin control by means of figures, the statistics and clinical records of the patients in this study cause the author to conclude that all types of patients do as well on a single dose of globin insulin each day as on other kinds of insulin, whether alone or in combination. It is easier to adjust the dose of G. I. than with the varying combinations of P. Z. I. and S. I. Opportunities for mistakes in measuring doses are greatly decreased as compared with multiple daily doses or combinations. It is also easier to instruct a patient in self-medication.

Liberation of Histamine by Curare. Editorial. *Brit. Med. J.* No. 4568:212 (1948). Several years ago it was observed that the injection of curare into the artery supplying the muscle of a dog's leg released a substance in the blood which acted like histamine. No practical significance was attached to this finding until the unusual effects from the injection of curare were observed in patients. Occasionally the intravenous injection of curare causes a transient fall of blood pressure which is accompanied by a feeling of warmth, giddiness, and headache. In a few cases there has been a severe fall in the blood pressure along with hemoglobin concentration.

Recent studies in human patients of the effects of curare on the cardiovascular system revealed that curare produced the same effects as did histamine. Curare was injected into the brachial artery below a pneumatic cuff which was inflated to 100 mm. for 2 minutes after the injection. When the cuff was released the forearm became hyperemic and engorged. Numerous areas of purple discoloration appeared but they disappeared within 30 minutes. Following this the arm swelled with a firm edema which lasted for 16 to 36 hours. This injection of curare also caused an increase in the acid secretion in the stomach.

The view that curare liberated histamine was verified when it was found that the observed histamine-like effects obtained from the injection of curare could be diminished or abolished by the administration of antihistaminic substances such as pyribenzamine.

The effects described above were intensified because the curare was injected into the arterial system while normal therapeutic injections are given intravenously. Therefore, the reactions seen from the therapeutic injection of curare would be expected to be much milder.

BOOK REVIEW

The Sulfonamides and Allied Compounds. By Elmore H. Northey, Ph. D., Administrative Director, Stamford Research Laboratories, American Cyanamid Company, Stamford, Connecticut. A. C. S. Monograph Series No. 106. Reinhold Publishing Corporation, 330 West Forty-second Street, New York, N. Y., 1948. xxvii+660 pp. 15×23 cm. Price $12.50.

This monograph is an outgrowth of a review originally prepared and presented before the A. A. A. S., at the Research Conference in Chemistry held at Gibson Island, Maryland, July 1939. It was then expanded for the A. C. S. and published in Chemical Reviews in 1940. From that period on a great deal of chemical and clinical research took place on this type of compound and the present work is an attempt to summarize this material.

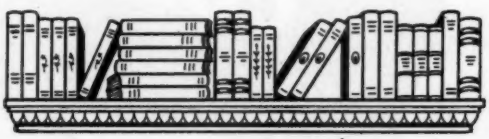
Following a brief history of bacterial chemotherapy, there follows a discussion of the nomenclature, classification and synthesis of sulfanilamide derivatives. This section summarizes the better methods of synthesis. The next five chapters correlate structure and activity of sulfanilamide derivatives and of sulfones and compounds related to them. There are extensive tabulations of the melting points, activities and references to the literature. H. J. White in Chapter VIII gives a good description of the various methods used in evaluating chemotherapeutic activity. He includes a table listing the response of various test organisms to certain sulfa drugs. The next chapter attempts to generalize on the relationship of structure to chemotherapeutic activity from the voluminous data presented previously. This section includes, also, a tabulation of the compounds which are and are not antagonized by p-aminobenzoic acid. J. T. Litchfield, Jr., summarizes the pharmacology of the sulfonamides and sulfones in the following chapter. The various theories of the mechanism of action of these substances are presented by Northey. The final chapter, edited by B. J. Carey, summarizes the extensive clinical experiences of those utilizing the sulfonamides and sulfones in therapy. It is not intended for the general practitioner or clinician

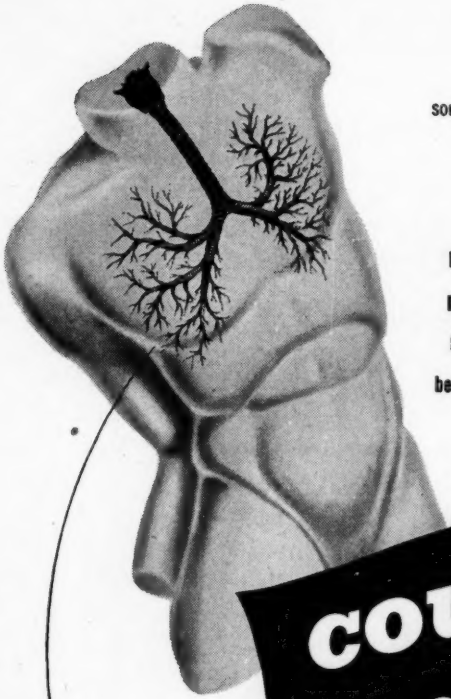
but to provide background for those engaged in experimental chemotherapy.

The appendixes include abbreviations used in the text, trade names for sulfanilamide, of which there are 61, and trade names, chemical names and formulas for sulfanilamide derivatives and related compounds.

As an indication of the completeness of the work it may be stated that there are 2668 references, although it is unfortunate that the literature search was not carried past January, 1945. The book should be extremely valuable to anyone doing research in, or wishing to locate information regarding, the sulfonamides and related compounds.

N. RUBIN





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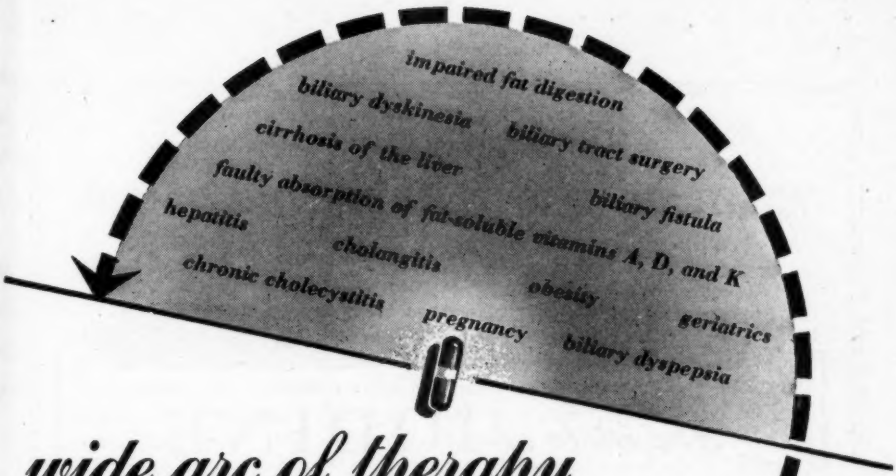

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